REMARKS

Applicants would like to take this opportunity to thank the Examiner for graciously holding an interview with the undersigned representative on June 15, 2004, which is recapitulated in the Interview Summary dated June 17, 2004. Claims 1-16 are cancelled herein without prejudice or disclaimer, and independent claim 17 and its dependent claims 18-32 are new. Claims 17-32 are introduced to cover potential commercial embodiments.

Basis for claims 17-32 is in the specification throughout and in the claims as originally filed. For example, basis for claim 17 is in claim 1 as originally filed; the specification at page 26, lines 1-6; and Table 13. In particular, the specification at page 26, lines 1-6 and Table 13 show haplotypes including three positions in a CYP2D6 flanking region can be utilized to predict a human's capacity to metabolize a CYP2D6 enzyme substrate from the entire range of capacities. This specification also shows that specific positions for these haplotypes can be replaced with other positions described in Table 10 on page 25 of the specification. Also, Table 2, Table 6, Table 7, Table 8 and Table 9 describe polymerase chain reaction oligonucleotides useful for identifying nucleotides at three or more polymorphic sites in a CYP2D6 flanking region. Table 10 shows haplotypes at seven positions in a CYP2D6 flanking region, and Table 13 is a representative guide for predicting a human's capacity to metabolize a CYP2D6 enzyme substrate from haplotypes that include three positions. Also, basis for claims 18-26, for example, is in claim 1 as originally filed and in portions of the specification previously mentioned. Basis for claims 27-29 is in Table 13, Table 12, Table 3 and Table 1, and claims 31-32 find basis in the specification on page 19, lines 1-8, for example.

Accordingly, the specification provides full support and working examples for the methods of claims 17-32, and offers several polymorphic site combinations useful for practicing these methods. Thus, the specification fully teaches the claimed methods.

The following addresses specific issues raised in the Office action.

Formal Matters

Applicants note the restriction and the species election requirement summarized in paragraphs 2 and 3 of the Office action. With respect to paragraph 4, Applicants submitted a certified copy of the priority document required by 35 U.S.C. §119(b) under separate cover on November 9, 2004. With regard to paragraph 5 of the Office action, Applicants acknowledge the citation correction for document "AN." With regard to paragraphs 6 and 7, the specification on page 3, line 1 has been amended to remove the embedded hyperlink. Applicants have reviewed the specification and determined that trademarks are designated appropriately with the symbol ® or ™ in accordance with MPEP § 608.01(v). Thus, all of the formal requirements presented in paragraphs 2-7 of the Office action have been addressed.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 9 were rejected under 35 U.S.C. § 112, second paragraph as certain claim terms allegedly were indefinite. For example, the Office objected to the term "for determining a human's capacity to metabolize a substrate of a CYP2D6 enzyme" as not being affirmatively specified, the term "the region" as it allegedly found no antecedent basis, and the term "said region is represented by a sequence as set forth in SEQ ID NO: 2" as the relationship between the region and SEQ ID NO: 2 allegedly was unclear. Because these terms are not present in new claims 17-32, cancellation of claims 1-16 renders moot the rejections under 35 U.S.C. § 112, second paragraph.

Applicants note that multiple positions in the CYP2D6 flanking region are specified in claims 18-26 according to positions known in the art and described, for example, in Table 2 of the specification. As these positions are referenced in the art, a person of ordinary skill can readily locate these positions in nucleic acids from different subjects.

Claim Rejections Under 35 U.S.C. § 102

Claims 1 and 9 were rejected under 35 U.S.C. § 102(b), § 102(a) and § 102(e) as allegedly being anticipated by Raimundo *et al,* European Journal of Clinical Pharmacology 55:A5 (1999) (Raimundo abstract), Raimundo *et al.*, Pharmacol. Genetics 10:577-581 (10/2000)

(Raimundo article), and WO 01/55432 published on August 2, 2001 and having an international filing date of January 30, 2001 (Raimundo patent application). It is respectfully submitted that these rejections are moot in view of the cancellation of claims 1-16 and the introduction of claims 17-32 for the reasons described hereafter.

The present patent application claims the benefit of United Kingdom Patent Application No. 0021286.0 filed on August 30, 2000. Accordingly, the Raimundo journal article, which published in October 2000, and the Raimundo patent application, which was filed on January 30, 2001 and published on August 2, 2001, are not clearly citable as prior art under 35 U.S.C. § 102(a) or § 102(e). The methods of claims 17-32, however, are not anticipated by the cited documents even if they are considered prior art, as described below.

Claims 17-32 are distinguished from the Raimundo abstract, journal article, and patent application for several reasons. Claim 17 specifies that the metabolic capacity of a CYP2D6 enzyme is predicted from the range of capacities in a human based upon nucleotides identified at three or more polymorphic sites in a CYP2D6 flanking region. These methods were elucidated in part by determining the value of haplotypes for predicting CYP2D6 metabolic capacities in a significant number of subjects, as presented in the Examples section of the present patent application. Performing these analyses lead to a discovery that haplotypes comprising three or more positions were useful for predicting a subject's capacity to metabolize a CYP2D6 substrate. As noted above, results are summarized in Table 13 on page 26, which shows haplotypes comprising three or more positions have a significant predictive value of 74% or more across a full range of capacities.

None of the Raimundo documents clearly disclose or enable the claimed methods as the studies reported therein stop short of those required for arriving at the claimed methods. The Raimundo abstract mentions seven point mutations were identified in the CYP2D6 promoter at positions -234, -277, -590, -652, -1147, -1338 and -1496, but never determines whether haplotypes covering three or more of these positions are useful for predicting an individual's capacity to metabolize a CYP2D6 substrate. Given the small number of individuals tested (i.e., only 30

individuals), it could not be determined that haplotypes of three or more positions would have predictive value. Thus, the Raimundo article does not disclose or enable the claimed methods.

The Raimundo article also falls short of the claimed methods. The analysis in Table 1 of the Raimundo article, for example, maps haplotypes for a small number of individuals having particular metabolic capacities. The Raimundo article does not, however, determine the predictive value of these haplotypes. The article does not determine whether a significant percentage of individuals characterized by a particular haplotype also are characterized by a particular metabolic capacity phenotype. And as noted for the Raimundo abstract, even if this type of analysis was performed, it likely would not be meaningful since very few subjects were studied and it could not be determined that haplotypes of three or more positions would have predictive value. Although the article mentions in its abstract that a genotype at a single position, position -1496, might possibly identify over 60% of intermediate metabolizers in Caucasian populations, the article does not disclose, teach or suggest methods for predicting metabolic capacity based upon a haplotype of three or more positions. Stated another way, the article did not mention a haplotype of three or more polymorphic sites should be selected over a haplotype of one, two or more, four or more, or five or more polymorphic sites, for example. The article also fails to disclose, teach or suggest a method of predicting a metabolic capacity from a full range of capacities (e.g., a range spanning ultraextensive metabolizer (UEM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) subjects), as discussed in greater detail hereafter. Because of these deficiencies, the article does not enable or disclose, teach or suggest the claimed methods.

The Raimundo patent application also does not anticipate the claimed methods. For example, Table 2 on page 20 reports genotype frequencies at individual polymorphic sites, but does not report haplotypes. Table 3 on page 26 reports a genotype at one position in the CYP2D6 promoter, position -1584, but it does not determine the predictive value of the position, nor does it determine a predictive value in conjunction with two or more other positions. The document therefore does not disclose, teach or suggest a predictive method in which nucleotides are identified at three or more positions. Thus, the Raimundo patent application also fails to anticipate the claimed methods.

As mentioned above, none of the Raimundo documents disclose, teach or suggest methods in which the metabolic capacity is predicted from the range of capacities in humans. For example, the Raimundo abstract mentions PM and EM subjects, and does not discuss UEM or IM subjects. The Raimundo journal article discusses EM, IM and PM subjects but does not mention UEM subjects, and the Raimundo patent application discusses IM and UEM subjects but does not significantly characterize EM or PM subjects. Thus, none of the Raimundo documents disclose, teach or suggest methods for predicting an individual's metabolic capacity within the range of capacities in humans.

Further, the methods described in claims 17-32 offer advantages over the methods described in the Raimundo documents. Specifically, the Raimundo journal article mentions that detecting a genotype at one position, position -1496, might be useful for identifying 60% of IM subjects. In contrast, methods in claims 17-32 have a higher resolution power and are more discriminatory as evidenced by a minimum resolution power of 74% disclosed in Table 13 of the specification on page 26.

Accordingly, the Raimundo documents do not enable or disclose, teach or suggest the methods of claims 17-32, and it is respectfully requested that the Office withdraw the rejections under 35 U.S.C. §102.

CONCLUSIONS

Claims 1-16 are cancelled herein without prejudice or disclaimer and claims 17-32 are new. Applicants respectfully assert that the cancellation of claims 1-16 obviates the indefiniteness rejections of claims 1 and 9 under 35 U.S.C. §112, second paragraph, and render moot the rejections under 35 U.S.C. §102 in view of the Raimundo documents. As all outstanding rejections are obviated by the introduction of new claims 17-23 and the cancellation of claims 1-16, it is respectfully requested that the Office issue a notice of allowance for claims 17-32.

If it is believed that further discussions would advance prosecution, the Examiner is encouraged to contact the undersigned representative by telephone. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to the credit card designated in the attached PTO-2038 referencing docket no. SGL-2019-UT.

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Respectfully submitted,

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